CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074868

Trade Name : OXYBUTYNIN CHLORIDE SYRUP USP 5MG/5ML

Generic Name: Oxybutynin Chloride Syrup USP 5mg/5ml

Sponsor : Morton Grove Pharmaceuticals, Inc.

Approval Date: February 12, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074868

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Chemistry Review(s)	X			
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Pharmacology Review(s)				
Statistical Review(s)				
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Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074868

APPROVAL LETTER

ANDA 74-868

Morton Grove Pharmaceuticals, Inc.
Attention: Maurice E. Bardoni
6451 West Main Street
Morton Grove, IL 60053

Dear Sir:

This is in reference to your abbreviated new drug application dated March 20, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxybutynin Chloride Syrup USP, 5 mg/5 mL.

Reference is also made to your amendments dated January 16, and February 3, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Oxybutynin Chloride Syrup USP, 5 mg/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ditropan® Syrup, 5 mg/5 mL of Hoechst Marion Roussel, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

2/12/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-868
Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

1/31/97

HFD-625/M.Shaikh/1-29-97
HFD-625/M.Smela/1-29-97 1/31/97
HFD-617/S.O'Keefe/PM/1-30-9 1/31/97
HFD-620/A.Rudman/
HFD-613/J.Grace/ 1/31/97
HFD-613/C.Holquist
x:\new\firmsam\morton\ltrs&rev\74868app.ltr
F/T by: bc/1-30-97

APPROVED

Letter revised to include chemistry amendment. 2/3/97

2/4/97

2/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074868

FINAL PRINTED LABELING

Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

OXYBUTYNIN CHLORIDE SYRUP, USP
5 mg/5 mL
PRODUCT CODE 8092
FINAL PRINTED 1 PINT (473 mL) PLASTIC CONTAINER LABELING

MGP

NDC 60432-092-16

OXYBUTYNIN CHLORIDE SYRUP, USP
5 mg/5 mL

Each teaspoonful (5 mL) contains:
5 mg oxybutynin chloride

DO NOT USE THIS CONTAINER IF THE SAFETY RING AT THE BOTTOM OF THE CAP IS DETACHED OR LOOSE.

BULK CONTAINER — NOT FOR HOUSEHOLD USE

CAUTION: Federal law prohibits dispensing without prescription.

NET: 1 Pint (473 mL)

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

PHARMACIST: Dispense in tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured By: Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

50-8092-16
ISS 8/96

PATIENT INFORMATION: See accompanying package insert.

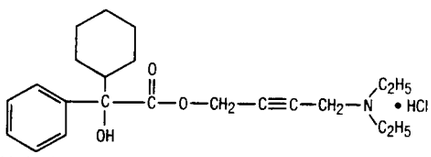
3 60432-092-16 6

OXYBUTYNIN CHLORIDE SYRUP, USP 5 mg/5 mL

FEB 12

DESCRIPTION

Chemically, oxybutynin chloride is 4-(Diethylamino)-2-butynyl (±)-α-phenylcyclohexaneglycolate hydrochloride. The molecular formula of oxybutynin chloride is $C_{22}H_{31}NO_3$•HCl. The structural formula appears below:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.96. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Each 5 mL, for oral administration, contains 5 mg of oxybutynin chloride. In addition, the following inactive ingredients are present: Artificial raspberry flavor; citric acid, USP; D&C Yellow No. 10; FD&C Blue No. 1; glycerin, USP; liquid sugar; methylparaben, NF; propylene glycol, USP; sodium citrate, USP and sorbitol solution, USP.
Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).
Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.
Oxybutynin chloride was well tolerated in patients administered the drug in controlled studies of 30 days duration and in uncontrolled studies in which some patients received the drug for 2 years. Pharmacokinetic information is not currently available.

INDICATIONS AND USAGE

Oxybutynin chloride syrup is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (ie, urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

Oxybutynin chloride is contraindicated in patients with untreated angle closure glaucoma and in patients with untreated narrow anterior chamber angles since anticholinergic drugs may aggravate these conditions.
It is also contraindicated in partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis, and myasthenia gravis. It is contraindicated in patients with obstructive uropathy and in patients with unstable cardiovascular status in acute hemorrhage.
Oxybutynin chloride is contraindicated in patients who have demonstrated hypersensitivity to the product.

temperature, can cause heat prostration (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy, or colostomy. In this instance treatment with oxybutynin chloride would be inappropriate and possibly harmful.
Oxybutynin chloride may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.
Alcohol or other sedative drugs may enhance the drowsiness caused by oxybutynin chloride.

PRECAUTIONS

Oxybutynin chloride should be used with caution in the elderly and in all patients with autonomic neuropathy, hepatic or renal disease. Oxybutynin chloride may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy.
Administration of oxybutynin chloride to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.
Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at dosages up to approximately 400 times the recommended human dosage showed no evidence of carcinogenicity.
Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.
Pregnancy: Teratogenic Effects-Pregnancy Category B. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.
Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.
Pediatric Use. The safety and efficacy of oxybutynin chloride administration have been demonstrated for pediatric patients 5 years of age and older (see **DOSAGE AND ADMINISTRATION**). However, as there is insufficient clinical data for pediatric patients under age 5, oxybutynin chloride is not recommended for this age group.

ADVERSE REACTIONS

Following administration of oxybutynin chloride, the symptoms that can be associated with the use of other anticholinergic drugs may occur:
Cardiovascular: Palpitations, tachycardia, vasodilatation
Dermatologic: Decreased sweating, rash
Gastrointestinal/Genitourinary: Constipation, decreased gastrointestinal motility, dry mouth, nausea, urinary hesitance and retention
Nervous System: Asthenia, dizziness, drowsiness, hallucinations, insomnia, restlessness
Ophthalmic: Amblyopia, cycloplegia, decreased lacrimation, mydriasis
Other: Impotence, suppression of lactation

OVERDOSAGE

The symptoms of overdosage with oxybutynin chloride may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (eg, restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis, and coma.
In the event of an overdose or exaggerated response, treatment should be symptomatic and supportive. Maintain respiration and induce emesis or perform gastric lavage (emesis is contraindicated in precomatose patients, convulsive or psychotic state). Activated charcoal may be administered as well as a cathartic. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and sponges.

DOSAGE AND ADMINISTRATION

Adults: The usual dose is one teaspoonful (5 mg/5 mL) syrup two to three times a day. The maximum recommended dose is one teaspoonful (5 mg/5 mL) syrup four times a day.
Children over 5 years of age: The usual dose is one teaspoonful (5 mg/5 mL) two times a day. The maximum recommended dose is one teaspoonful (5 mg/5 mL) three times a day.

HOW SUPPLIED

Oxybutynin Chloride Syrup, USP 5 mg/5 mL is a light aqua, raspberry-flavored liquid supplied in 1 Pint (473 mL) bottles.

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15 °-30 °C (59 °-86 °F).

Caution: Federal law prohibits dispensing without prescription.

Product No.: 8092

Manufactured By:
Morton Grove Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074868

CHEMISTRY REVIEW(S)

Addendum to Chemist's Review # 3

ANDA 74-868

1. Chemistry issues were previously closed per Review # 3 for this ANDA.

2. Allen Rudman called the firm regarding the liner for HDPE bottle which is described as or equivalent. After having conversation with Allen, firm withdrew the phrase for an equivalent liner. Firm submitted a telephone amendment on 2-3-97. According to this amendment, the firm modified the description of the closure liner used for the 16 oz glass bottle and the 16 oz HDPE bottle on pages 393 and 394 of the original submission. The word "or equivalent" have been eliminated. The replacement pages are enclosed.

Conclusion: The ANDA remains approvable.

c.c: AND 74-868
Division File
Field Copy

Endorsements:

HFD-625/MShaikh/ 2/4/97
HFD-625/MSmela/

x:\new\firmsam\morton\ltrs&rev\74868rv3.add

2/4/97

1. *CHEMIST's REVIEW # 3*

2. **ANDA 74-868**

3. NAME AND ADDRESS OF APPLICANT
Morton Grove Pharmaceutical, Inc. (MGP)
6451 West Main Street
Attention: Maurice E. Bardoni
Morton Grove, IL 60053
tel. 708 967-5600, fax 708 967-2211

4. BASIS OF SUBMISSION
Innovator's Product Name: *Ditropan Syrup* by
Marion Merrell Dow, Inc.
(now Hoechst Marion Rssl.)

5. SUPPLEMENT:
N/A

6. PROPRIETARY NAME:
None used

7. Non-PROPRIETARY NAME:
Oxybutynin Chloride Syrup, USP
5 mg/5 mL

8. Supplement Provides For:
N/A

9. AMENDMENTS & Other DATES.
A. **FIRM:**
Original submission: 03-20-96
NC: 3-27-96 (revised form 356h).
NC: 05-03-96 (revised pages 2, 18, & 58)
Major Amendment: 9-17-96 (Response to 7-30-96 NA letter)
* Facsimile Amendment: 1-16-97

B. **FDA:**
FDA acceptance of ANDA: 4-10-96
Bio Acceptance letter: 7-5-96
NA letter (Chemistry + Labeling): 7-30-96
NA Facsimile (Labeling): 1-10-97

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of bladder instability, anti-cholinergic

11. Rx or OTC:
Rx

12. RELATED IND/ANDA/DMF:

13. DOSAGE FORM: Syrup

14. POTENCY: 5 mg/5 mL

15. CHEMICAL NAME: $C_{22}H_{31}NO_3 \cdot HCl$
D,L-4-diethylamino-2-butynlphencyclohexylglycolate HCl salt drug substance
[*1508-65-2*]
MW = 393.96

16. Records & Reports:
N/A

17. COMMENTS.
MGP submitted adequate information to support this ANDA with respect to adequate status of the referenced for , adequate controls for raw material and finished dosage form per USP 23 and OGD requirements, stability of the drug product, acceptable bio status and FPL, and all the supporting information for the marketplace container/closure system. cGMP status is okay per EER dated 5-18-96.

18. CONCLUSIONS & RECOMMENDATIONS:
Approved.

19. Reviewer: Mujahid L. Shaikh

Date Completed: 1-28-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074868

BIOEQUIVALENCE REVIEW(S)

ANDA 74-868

JUL 3 1996

Morton Grove Pharmaceuticals
Attention: W.F. Hendershot, Ph.D.
6451 West Main Street
Morton Grove IL 60053

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxybutynin Chloride Syrup, 5 mg/5 mL in 1 pint.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 1 1996

Oxybutynin Chloride
Syrup, 5 mg/5 mL in 1 pint
ANDA # 74-868
Reviewer: Man M. Kochhar
74868W.396

Morton Grove Pharmaceuticals.
Morton Grove, Illinois
Submission Date:
March 20, 1996

Review of a Waiver Request

The Firm has requested a waiver of in vivo bioequivalence study for its oxybutynin chloride syrup 5 mg/ 5 mL, in 1 pint bottle, based upon 21 CFR 320.22 (b)(3).

Comparative Formulation

Ingredients	Morton Grove Pharmaceuticals	Marion Merrell Dow Inc.
Oxybutynin Chloride	5.0 mg/5 mL	5.0 mg/5 mL
Methylparaben, NF		
Citric Acid, anhydrous, USP		
Sodium Citrate		
Glycerine		
Sorbitol Solution, USP		
Sucrose		
Flavor		
Dye FDC Green # 3		
Propylene Glycol		
FD&C Blue # 1		
D&C Yellow # 10		
Purified Water, USP Q.S.to		
10% Citric Acid Solution		
10% Sodium Citrate Solution		

Batch Size:

Deficiency: None

Comments:

1. The formulation of the test product and the innovator product oxybutynin chloride (Ditropan; Marian Merrell) is similar in concentration of active ingredients. The inactive ingredients vary but within the limits of FDA Inactive Ingredient guide. The quantities of sodium citrate and citric acid varies because at the end the test product uses solutions of sodium citrate and citric acid to adjust the pH. Methyparaben is . These are within the limits of the inactive ingredient guide of FDA. The glycerine content in Ditropan Syrup is while it is in oxybutynin chloride syrup. Since the amount of glycerine is less in the test product than in the reference product, there should

be no safety concern. It is probable that PG present in the test product will compensate for the lowered amount of glycerin in terms of cosolvency. The sucrose , sorbitol solution, and flavor are same in both products.

2. Propylene glycol (PG) is used at the level to dissolve methylparaben. The use of this solvent in liquid dosage form for that purpose is well documented. An example is Sandoz's Tavist syrup. There are no published reports of PG interfering with the absorption of oxybutynin chloride

3. To match the brand color "light aqua or green blue", the test product use a combination of FD&C Blue # 1 and D&C yellow # 10 instead of FD&C Green # 3 as in Ditropan. Both these colors are approved by FDA and commonly used in liquid dosage forms.

4. The dosage form, route of administration, strength (5 mg/5 mL) and labeling of the test drug product are identical to those of the innovator product. The dosages of the test and reference products are same.

4. From the bioequivalence point of view, the waiver of in vivo bioequivalence study requirement should be granted based on 21 CFR 320.22 (b)(3).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Morton Grove Pharmaceuticals Inc. on its Oxybutynin Chloride Syrup 5 mg/5 mL, in 1 pint bottle falls under 21 CFR 320.22 (b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for 5 mg/5 mL Oxybutynin Chloride Syrup (test product) in 1 pint bottle is granted.

From the bioequivalence point of view, the Division of Bioequivalence deems the test syrup of Oxybutynin Chloride 5 mg/5 mL in 1 pint bottle to be bioequivalent to Ditropan 5 mg/5 mL, manufactured by Marrion Merrell Dow Inc.

The firm should be informed of the recommendation.